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IN THE CLAIMS:

1- 22 (Cancelled)

23. (Currently amended) A method of detecting a binding event involving a test protein with a test ligand, the method comprising:

(a) providing an unpurified test protein;

(b) providing a test ligand;

(c) contacting the test ligand with the unpurified test protein to form a test mixture;

(d) contacting the test mixture with an exchange buffer comprising a denaturant and deuterium, the exchange buffer having a denaturant concentration;

(e) contacting the test mixture with a mass spectrometry matrix medium;

(f) determining a change in mass of the test protein by mass spectrometry;

(g) varying the denaturant concentration of the exchange buffer;

(h) repeating steps (a)-(g) a desired number of times; and

(i) analyzing the change in mass of the test protein as a function of denaturant concentration, whereby a binding event involving the test protein and the test ligand is detected.

24. (Original) The method of claim 23, wherein the test protein is disposed in a crude cell lysate.

25. (Original) The method of claim 23, wherein the test protein is associated with a disease phenotype.

26. (Original) The method of claim 23, wherein the disease phenotype is characterized by protein misfolding.

27. (Original) The method of claim 23, wherein the test protein has a mass of less than 1,000,000 daltons.

28. (Original) The method of claim 23, wherein the test protein is a multimeric protein.

29. (Original) The method of claim 23, wherein the test protein is disposed on a microtiter plate.

30. (Original) The method of claim 29, wherein a plurality of test proteins are disposed on the microtiter plate.

31. (Original) The method of claim 30, wherein the method further comprises the step of repeating steps (a)-(i) for each test protein disposed on the microtiter plate.

32. (Original) The method of claim 23, wherein the test protein is provided in picomolar or greater amounts.

33. (Original) The method of claim 23, wherein the test protein is *in vivo*.

34. (Original) The method of claim 23, wherein the denaturant is a chemical denaturant.

35. (Original) The method of claim 34, wherein the denaturant is selected from the group consisting of detergents, guanidinium chloride and urea.

36. (Original) The method of claim 23, wherein the mass spectrometry matrix material is a MALDI mass spectrometry matrix material and the mass spectrometry is MALDI mass spectrometry.

37. (Original) The method of claim 36, wherein the MALDI mass spectrometry matrix material is selected from the group consisting of sinapinic acid, α-cyano-4-

hydroxycinnamic acid, 2,5-dihdroxybenzoic acid, 2,5-dihydroxyacetophenone and 3-amino-4-hydroxybenzoic acid.

38. (Currently amended) The method of claim 23, wherein the analyzing comprises:

(a) plotting the change in mass of the test protein in the presence of the test ligand as a function of denaturant concentration to generate a first denaturation curve;

(b) plotting the change in mass of the test protein in the absence of the test ligand as a function of denaturant concentration to generate a second denaturation curve; and

(c) identifying a change in the ~~position~~ transition midpoint of the first denaturation curve relative to the ~~position~~ transition midpoint of the second denaturation curve, wherein a difference in the ~~positions~~ transition midpoints of the first and second denaturation curves is indicative of a binding event involving the test ligand and the test protein.

39. (Original) The method of claim 23, wherein the analyzing is performed using a computer program.

40. (Original) The method of claim 23, further comprising providing a reference protein with the test protein.

41-124. (Cancelled).

125. (New) A method of detecting a binding event involving a test protein with a test ligand, the method comprising:

(a) providing a test protein;

(b) providing a test ligand;

(c) contacting the test ligand with the test protein to form a test mixture;

(d) contacting the test mixture with an exchange buffer comprising a denaturant and deuterium for a specified time of exchange (t), the exchange buffer having a denaturant concentration;

(e) contacting the test mixture with a mass spectrometry matrix medium;

(f) determining a change in mass of the test protein by mass spectrometry;

(g) varying the denaturant concentration of the exchange buffer;

(h) repeating steps (a)-(g) a desired number of times; and

(i) analyzing the change in mass of the test protein as a function of denaturant concentration and the specified time of exchange (t), whereby a binding event involving the test protein and the test ligand is detected.

126. (New) The method of claim 125, wherein the test protein is an unpurified test protein.

127. (New) The method of claim 125, wherein the detecting of a binding event further comprises fitting data comprising a change in mass of the test protein as a function of denaturant concentration and the specified time of exchange (t) to the equation $C_{1/2}^{SUPREX} = C_{1/2}^{den} - (RT/m) \ln(\langle k_{int} \rangle t/0.693 - 1)$.